REPORT OF WORKSHOP ON

NATURALLY OCCURRING SUBSTANCES IN TRADITIONAL AND BIOTECHNOLOGY-DERIVED FOODS: THEIR POTENTIAL TOXIC AND ANTITOXIC EFFECTS

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ARNOLD AND MABEL BECKMAN CENTER
IRVINE, CALIFORNIA
MARCH 10-11, 1992

UNITED STATES DEPARTMENT OF AGRICULTURE
COOPERATIVE STATE RESEARCH SERVICE
WASHINGTON, DC 20250

July 28, 1992

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ACKNOWLEDGEMENTS

The role of Dr. Steve Taylor of the University of Nebraska must be acknowledged, for it was he who brought together the separate efforts of the Cooperative State Research Service (CSRS) and the Food and Nutrition Board (FNB) and made this cooperative effort possible.

Appreciation is expressed to Dr. Catherine Woteki, Director of the FNB, for her cooperation and collaboration in this endeavor. Thanks is also extended to Sheila Mylet and Marcia Lewis of the FNB staff for their assistance in ensuring the smooth execution of this meeting.

Grateful appreciation is extended to my colleagues Dr. Sandy Bigelow (currently with Pfizer, Inc.) for his assistance in planning this meeting and Dr. Bernie Liska (Purdue University) for his assistance in monitoring the workshop and assembling this report. Dr. Jack Barnes, currently on detail from USDA to the National Acid Precipitation Assessment Program (NAPAP) under the Executive Office of the President, was a partner in this effort until his reassignment in July of 1991. The contribution of the workshop session discussion leaders and rapporteurs was crucial and appreciation is expressed for their efforts.

Finally, but hardly least, the foresight demonstrated by the Committee of Nine, the advisory and oversight body for regional research administered by CSRS, in recommending funding in partial support of this planning meeting is gratefully acknowledged. Also, the willingness of the University of California Agricultural Experiment Station to act as a liaison between CSRS and the FNB is appreciated.

EXECUTIVE SUMMARY

A. Background

A one-and-a-half day workshop sponsored by the U.S. Department of Agriculture's Cooperative State Research Service (CSRS) was held in Irvine, California, on March 10-11, 1992. The workshop immediately followed, and was planned in cooperation with, a symposium sponsored by the National Academy of Sciences Food and Nutrition Board (FNB). The topic of the symposium and workshop was "Naturally Occurring Substances in Traditional and Biotechnology-Derived Foods: Their Potential Toxic and Antitoxic Effects."

It was proposed that the toxicants to be addressed in this workshop should be those chemical substances that occur naturally if foods or that may be formed from naturally occurring compounds as a result of cooking or processing and which cause or pose adverse health consequences in humans when consumed in food. Mycotoxins and phycotoxins were included because they are generally considered naturally occurring under a wide range of environmental conditions. Bacterial food toxins, environmental contaminants, and manmade additives were proposed as not being within the scope of this workshop. Antitoxicants are those naturally occurring chemical substances in foods that appear to mitigate the effects of certain human disorders. The workshop considered the effects of genetic engineering of food plants and animals and biotechnologically-derived foods on the levels of toxicants and antitoxicants in foods.

Sixty-two workshop participants from agricultural research, food and nutrition research, and public health research communities affiliated with government, universities, and private sector organizations elucidated issues and research objectives in five breakout sessions relating to 1) the impact of genetic engineering and biotechnology, 2) relative risks and benefits, 3) reducing risks, 4) antitoxicants, and 5) analytical considerations. The findings and recommendations of the workshop participants will be used by the CSRS in planning research directions in this area and should be useful to the FNB as it explores the potential for establishing a committee to review current information on this topic and to recommend research direction.

B. Issues and Research Objectives

Major issues and research objectives identified for each breakout session are summarized as follows:

I. Impact of Genetic Engineering/Biotechnology

Issues

1. How to determine which toxic compounds or antitoxic compounds should have priority for reduction or enhancement using genetic engineering approaches in food crops?

2. What is the risk/benefit of a genetically altered food, derived either by traditional plant breeding or genetic engineering?

3. What information is needed to assess the safety of a new genetically engineered food (such as a tomato)?

4. How can food safety issues be separated from social issues related to genetically altered foods?

5. What approaches should be used to inform the public about the risk/benefit of genetically altered foods?

Research Objectives

1. Develop molecular and cellular techniques for genetic alteration of plants to optimize antitoxic compounds and reduce levels of toxic compounds.

2. Develop methods to assess the safety of genetically altered crops or animals in regard to chemical composition, and biological effects.

3. Improve approaches to determine risk/benefit of biotechnology-derived foods.

4. Develop methods to identify toxicants and antitoxicants important to human health where levels can be modified in genetically engineered foods.

II. Relative Risks and Benefits

Issues

1. The diet is not only a source of nutrients and energy but is also a source of toxic challenge to man.

2. Natural constituents of foods that either promote disease or protect against disease must be considered in determining risk/benefit values for food.

3. Simple summation of risk/benefit from individual toxicants or antitoxicants in food does not reflect the toxic/antitoxic impact of whole foods (constituent risk does not equal true risk of whole foods).

4. How do we assess the risk or benefit of natural toxicants and anitoxicants? We can't use the same approach we use for food additives and contaminants.

Research Objectives

1. Develop methods for assessing risks/benefits of toxic/antitoxic constituents of foods and mixtures of foods vs. toxicology testing of individual chemicals.

2. Determine the impact of diet on the immune system vs. toxicity for humans.

3. Integrate chemical analysis and biological assay to determine risks/benefits of natural toxic/antitoxic constituents of foods.

4. Improve the understanding of basic cellular and molecular mechanisms of toxicity/antitoxicity to improve overall risk assessments on natural food constituents.

III. Reducing Risks from Naturally Occurring Toxicants

Issues

1. There is a need to assemble and organize available information on natural toxicants regarding dietary food components, occurrence of compounds in foods, physical attributes of compounds, and physiological activitity (beneficial and adverse) of the compounds. This should also identify data gaps for future research.

2. What approaches can be used to prevent, reduce or eliminate risks due to naturally occurring toxicants in foods?

3. What environmental or ecological conditions result in the formation of naturally occurring toxicants in foods, specifically mycotoxins and phycotoxins?

Research Objectives

1. Improve understanding of how production methods can be used to prevent formation of natural toxicants in foods.

2. Develop rapid screening procedures to monitor the food supply in order to identify and remove contaminated food products.

3. Develop processing procedures to remove and/or inactivate toxicants in foods.

4. Develop alternate processing methods to eliminate processing-induced food toxicants.

5. Study nonconventional approaches to reduce adverse health effects of natural toxicants on humans.

IV. Antitoxicants

Issues

1. What diseases are subject to mitigation and what population groups should be targeted?

2. What are the best approaches for identifying and testing mitigating agents?

3. How important are in-depth studies of mechanisms, toxic and mitigating potency, and human safety of mitigating agents?

4. How are mitigating agents and natural and designed foods that contain these agents to be regulated?

5. How should the public be educated in a rational, nonadvocative manner on the role of mitigating agents (foods) in a healthy lifestyle?

Research Objectives

1. Better understand the potential of mitigating agents (food antitoxicants) to prevent or reduce severity of diseases other than cancer.

2. Identify new mitigating agents for cancer.

3. Define mechanisms of action (physiological, physiochemical, cellular and/or biochemical) for potential mitigating agents.

4. Establish dose-response efficacy for cancer inhibition as well as potentially harmful effects or cancer enhancement for promising mitigating agents and mixtures.

5. Develop an information database system containing available data on potential mitigating agents in specific food items.

6. Conduct a broad based study to test the role of dietary antioxidants and other tumor-suppressors as cancer mitigating agents. This research should include studies of mechanisms of action, safety and dose response, and levels of antioxidants in foods normally consumed.

V. Analytical Considerations

Issues

1. Changes occurring in foods because of genetic changes by either traditional crossbreeding or genetic engineering must be chemically identified.

2. Known toxicant/antitoxicant components of established foods must be determined in genetically altered foods and the levels present compared to known levels in the established foods.

3. Genetically altered foods must be "fingerprinted" for compounds below a molecular weight of 5000. Compounds showing significant changes must be chemically identified.

4. Analytical and structural identification infrastructure related to the determination of toxic/antitoxic chemicals in food does not exist.

5. A central coordinated database for toxic/antitoxic chemicals in foods needs to be developed.

Research Objectives

1. Improve analytical methods for determination of naturally occurring toxic/antitoxic constituents in established or genetically altered foods.

2. Develop new techniques for "fingerprinting" the components of foods.

Conclusions from Workshop

The workshop participants concluded that the topic of naturally occurring toxicants and antitoxicants in foods warrants a national research effort and national coordination. Targeted and multifaceted funding should be sought to undertake a coordinated multidisciplinary and interdisciplinary research effort involving agricultural production scientists, food and nutrition scientists and public health scientists from government, universities, and the private sector. Information should be coordinated and international linkages sought. Achieving a better understanding of the mechanisms and impacts of pharmacologically active, naturally occurring substances in foods will allow development of beneficial production and processing practices, recommendations for dietary intakes, and enhance the public's confidence in the food supply.

INTRODUCTION

Researchers have found that some naturally occurring substances in foods may have adverse or beneficial effects on human health when consumed, depending on dose and other factors. Most scientists' estimations indicate that naturally occurring toxicants rank below microbial contaminants and above chemical residues as threats to health from the food supply. The report of a 1988 workshop on food safety sponsored by the Institute of Food Technologists (IFT) concluded that, "Next to microbiological contaminants, naturally-occurring toxicants may represent the most significant hazard in the food supply" (IFT, 1989). Yet this topic has received relatively little attention and support compared to foodborne disease and pesticide residues.

The genetic engineering of food plants and animals and the production of food ingredients through biotechnology pose the possibility of incidental alteration in the levels or composition of naturally occurring toxicants in foods. The International Food Biotechnology Council (IFBC) states in a 1990 report that "...naturally occurring toxicants are and will remain the primary safety concern accompanying products of any genetic modification, by traditional or newer means" (IFBC, 1990). According to the Government Accounting Office, FDA considers foods produced by biotechnology or other novel means as their number one critical food safety issue (Wolf, 1992). The Environmental Defense Fund has called for FDA to establish regulations for the safety of genetically engineered foods, including a requirement for manufacturers of such foods to to notify FDA of the composition of the foods to ensure the absence of potentially dangerous components (Food Chemical News, 1991). The FDA, in a recent policy statement on foods derived from new plant varieties, including plants developed by recombinant DNA techniques, proposed to regulate these new plant varieties or their products as it does foods developed by traditional plant breeding (FDA, 1992).

Equally important is the growing field of knowledge regarding the beneficial health effects of many naturally occurring components of foods. The National Cancer Institute's five-year "Designer Foods" initiative will investigate the role of many of these substances in preventing cancer (Caragay, 1992). A nonprofit corporation in New Jersey is promoting economic and regulatory reforms in the U.S. to allow for development and marketing of "nutraceuticals," foods or food components that provide medical or health benefits (Pszczola, 1992). Confounding the issue, however, is the finding that some compounds can act as toxicants or antitoxicants, depending on dose and other factors.

BACKGROUND

The workshop was sponsored by USDA's Cooperative State Research Service (CSRS) in cooperation with the National Academy of Science's Food and Nutrition Board (FNB) and was held immediately following a one-and-a-half day symposium on the same topic sponsored by the FNB. The program for the symposium and workshop is attached (Appendix).

It was proposed that the toxicants to be addressed in this workshop should be those chemical substances that occur naturally in foods or that may be formed from naturally occurring compounds in foods as a result of cooking or processing and which cause or pose adverse health consequences in humans when consumed in food. Mycotoxins and phycotoxins were included because they are generally considered naturally occurring under a wide range of environmental conditions. Bacterial food toxins, environmental contaminants, and manmade additives were proposed as not being within the scope of this workshop. Antitoxicants are those naturally occurring chemical substances in foods that appear to mitigate the effects of certain human disorders. The workshop considered the effects of genetic engineering of food plants and animals and biotechnologically-derived foods on the levels of toxicants and antitoxicants in foods.

Sixty-two people participated in the workshop. The participants included agricultural research scientists, food and nutrition scientists, and public health scientists. Participant affiliations included universities, government, medical schools, industry and consultants, and foundations. Though the majority were from the United States, there were also participants from Canada and England. (See attached lists for participants in various breakout groups.)

Participants were asked to choose one of six workshop breakout sessions in which to participate:

1) Known Toxicants;
2) Impact of Genetic Engineering and Biotechnology on Naturally Occurring Toxicants and Antitoxicants in Foods;
3) Relative Risks and Benefits;
4) Reducing Risks from Naturally Occurring Toxicants;
5) Antitoxicants;
6) Analytical Considerations for Naturally Occurring Toxicants and Antitoxicants.

The session on **Known Toxicants** was combined with the session on **Relative Risks and Benefits**. The participants were asked to:

1) elaborate the issues surrounding the topic of the breakout session;
2) assess the base of knowledge and available information;
3) develop research objectives;
4) prioritize the research objectives;
5) identify potential participants in a coordinated research project;

6) identify potential funding mechanisms to undertake the research;
7) develop recommendations for further actions.

The breakout groups then reconvened and reported their recommendations to the full group. The following reports capture the discussions and recommendations of the workshop groups.

REPORTS FROM WORKSHOP GROUPS

I. IMPACT OF GENETIC ENGINEERING AND BIOTECHNOLOGY ON NATURALLY OCCURRING TOXICANTS AND ANTITOXICANTS IN FOODS

Members of the workshop group expressed support for the conclusions of previous efforts to address the safety of biotechnology-derived products including food products (Committee on the Introduction of Genetically Engineered Organisms into the Environment, 1987; IFBC, 1990). These included the general conclusion that there is no evidence that unique hazards exist in the use of recombinant DNA or other biotechnology techniques in the development of products. Members reaffirmed that the precision and accuracy of most biotechnology methods and the detailed knowledge of both the DNA inserted and the gene products encoded represents a significant advance over traditional plant breeding.

Workshop group members identified a number of relevant issues, developed several research objectives, and identified a number of organizations that might serve as cooperators or potential sources of funding for research programs. The workshop group had very limited time to prioritize research needs in this area.

A. Issues

Workshop group members identified a number of issues relevant to the impact of genetic engineering and biotechnology on levels of toxicants and antitoxicants in foods. The issues fall into several categories such as data acquisition, identifying genes important in toxicant production, assessing tradeoffs of different approaches to changing food composition, providing incentives for orphan product development, and enhancing resources for human risk assessment. These issues are enumerated below.

1. Providing incentives and resources for the acquisition of food composition profiles, especially with regard to minor constituents.

2. Distinguishing toxicants from other constituents in chromatographic/mass spectra, immunological, enzymatic or other food composition profiles.

3. Identifying genes responsible for synthesis of natural toxicants in the food supply that present significant risk due to high potency or wide consumer exposure.

4. Identifying genes responsible for synthesis of antitoxicants that can ameliorate risks due to food toxicants that are significant because of high potency or wide consumer exposure.

5. Selecting the most appropriate modalities for changing food composition from among traditional breeding, food formulation processing, dietary supplementation, non-recombinant biotechnology, and genetic engineering.

6. Balancing risk reduction through lowering toxicant levels in plants against adverse agronomic and food safety effects through decreased pest resistance.

7. Balancing enhancement of detoxification enzymes against unintended activation of other enzyme systems.

8. Encouraging development of orphan products which do not have sufficient market potential or commercial incentive to spur development, support commercialization, and clear regulatory requirements.

9. Deploying resources rationally for the safety evaluation of biotechnology-derived foods compared to traditional foods.

10. Utilizing the new techniques of biotechnology and genetic engineering to enhance effective, rational food toxicological risk assessment.

B. Research Objectives

Workshop group members developed several research objectives for the application of biotechnology and genetic engineering to the enhancement of food safety. The research objectives tended to fall into groups such as the development of gene/molecular probes, protection of plants from mycotoxin-producing fungi, elucidation of antibiotic associations between organisms, and engineering of rumen and intestinal microflora. These objectives are listed below.

1. Enhance systems for acquisition, storage, retrieval, analysis, and comparison of chromatographic/mass spectra, immunological, enzymatic and other composition profiles of foods.

2. Identify genes and genetic regulatory mechanisms for toxicants and antitoxicants in plants used for human food and animal feed.

3. Develop lines of plants that are deficient in selected toxicants or positive for selected antitoxicants to facilitate comparative risk assessment and agronomic research.

4. Explore the feasibility of using antisense and ribozyme technology for decreasing levels of natural toxicants in food-producing plants.

5. Explore the feasibility of gene/molecular probes for toxicants in enhancing food safety.

6. Isolate genes associated with biosynthesis of major toxicants and antitoxicants and develop gene/molecular probes for them.

7. Characterize the genetic/molecular differences between strains of plants that are susceptible and resistant to the growth of mycotoxin-producing fungi.

8. Elucidate the genetic and molecular basis for resistance to fungal growth in plants.

9. Develop gene/molecular probes for strains of plants that are resistant to the growth of fungi that produce mycotoxins and other natural toxicants.

10. Develop methods for genetic intervention in the susceptibility of food-producing plants to fungal growth.

11. Isolate genes and develop molecular probes that help protect plants against mycotoxin-producing fungi, thereby building on past experience with enzymes such as chitinase and beta-glucanase.

12. Elucidate the genetic and molecular basis of antibiotic associations between organisms that could be useful in enhancing food safety.

13. Explore the feasibility of genetically engineering rumen and intestinal microflora to degrade plant toxicants.

C. Cooperating Organizations

Workshop group members identified several organizations that may serve as cooperators or potential sources of funding for research in food biotechnology. Prime among these were the co-sponsors of the Symposium and Workshops, the Food and Nutrition Board (FNB) of the National Research Council (NRC) and the USDA Cooperative State Research Service (CSRS). In addition, the Public Health Service (PHS), the National Institutes of Health (NIH) Nutrition Coordinating Committee, the International Life Sciences Institute (ILSI), and the International Food Biotechnology Council (IFBC), or a successor, were mentioned as possible cooperating organizations.

D. Biotechnology and Food Risk Assessment

Workshop group members briefly discussed the potential impact of the new techniques of biotechnology and genetic engineering on food risk assessment. Topics discussed included oncomouse/mutamouse technology and sub-organismal system culture techniques such as developing sensitized cell lines for in vitro screening, tissue culture, and in vitro organ system models. Workshop participants noted that other workshops and other scientific organizations are devoting considerable time and resources to these and similar issues.

Impact of Genetic Engineering and Biotechnology on
Naturally Occurring Toxicants and Antitoxicants in Foods

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II. RELATIVE RISKS AND BENEFITS

Workshop group members identified four main issues relating to the risks and benefits associated with naturally occurring substances in foods. As a general premise, it was recognized that the relative risks to the public from these components in the food supply, particularly the risks of chronic disease, have been and still are underestimated. It was felt that the frequently cited estimate of a 1 in 13 chance of dying from cancer from eating food is a reasonable approximation, and that funding for research into the role of naturally occurring substances is inconsistently low, with too much research and regulatory effort directed toward relatively minor problems such as food additives and pesticide residues.

A. Issues

1. The diet is not only a source of nutrients and energy, but is also a source of toxic challenge to man.

There are two components of diet: (1) agents that promote disease, and (2) agents that protect against disease. Both the risks and the benefits of natural constituents of food must be included in the potential value of foods containing them. This is unlike the way in which food additives or pesticides are currently evaluated. Food safety in the past has been largely food additive safety.

The role of macronutrients (fat, fiber, calories, etc.) must be addressed as components of food product safety and wholesomeness. Even though it was recommended that the workshop not consider macronutrients during its deliberations, this workshop group felt that the relative risks and benefits of naturally occurring substances in food cannot be accurately determined if macronutrients are ignored.

The salient point encompassed by this issue is that we cannot say that diet is a toxic challenge without looking at the total diet.

2. Simple summation of the risk from individual toxicants in food does not reflect the toxic impact of the whole food.

In other words, constituent risk does not equal true risk. Our current methodology, as applied for additives and residues, tends to overestimate the risk from the food supply. There are problems in extrapolating data collected from laboratory animals to man and from high doses to low doses, as well as the complications of multiple components. Foods are complex mixtures and their matrix will affect bioavailability of naturally occurring substances. There will be additional effects due to processing, the source of the foods, and the particular agricultural practices used in production of the food.

There is a need to move away from simplistic lists of toxicants, and the associated "knee jerk" reaction whenever one is found in food. We are "hung up" on regulatory aspects of food safety, and not on the science. We cannot evaluate natural constituents in the same way we study food additives or contaminants.

3. Communications are inadequate.

Improved data collection from actual human and animal cases is needed. Veterinary epidemiology and human epidemiology need both greater emphasis and greater interaction in order to identify real problems associated with food. We need to broaden the disciplines involved in the study of naturally occurring substances, and improve the communications between scientists working in different areas of research. The group considered that directors of institutes, experiment stations, and their affiliates could serve an important and effective role in coordinating interactions between disciplines. We cannot pursue food safety problems with analytical chemistry or biological assay separately; they must be integrated.

We need a centralized "home" for pulling together a knowledgeable information base related to naturally occurring substances. An international communications network needs to be established. There is a need for a body to perform a "CDC-type" function in information gathering. Third world countries, which have more easily identifiable food safety problems, could be a valuable resource- in effect a laboratory that would provide clues to the real, and especially chronic, problems that natural substances cause throughout the world.

4. Safety and wholesomeness of food are the key factors.

In order to continue meeting goals to improve safety and wholesomeness of foods, a number of important research questions must be pursued. Perhaps the most critical is to investigate the oxidation-antioxidation hypothesis of tumorigenesis. Can this hypothesis explain the origin of many of the cancers that affect humans, and, perhaps more importantly, can it explain why more people don't get cancer? What is the role of naturally occurring substances in food as both promoters of oxidative tumorigenesis or as antioxidants that prevent the eventual development of tumors?

B. Research Needs

The following points related to issue 1 should be included in research:

- safety testing of foods (i.e., mixtures) versus toxicology testing of individual components;

- safety assessment based on data from whole foods versus single chemicals;

- the impact of diet on the immune system vis a vis toxicity for man needs to be evaluated.

The same research needs listed above for the first issue also apply to issue 2, especially the need to assess safety of complex mixtures versus that of single chemicals.

A research objective relative to issue 3 should include mobilizing the information flow from relatively obscure sources and organizing the information sources that are currently available. Individuals or organizations who can develop contacts and pursue recommendations of this and future workshops must be identified. The proceedings of this symposium/workshop should be published and made available for scientists-at-large who are working or have interests in this area. A follow-up to this symposium/workshop should be held to continue planning after the recommended steps are taken.

Regarding issue 4, we need to validate and standardize methods for evaluating toxicity of food-containing substances. This is necessary if we are to compare toxicity of new food products, obtained through biotechnology or otherwise, with standard products. Biological tests to evaluate food wholesomeness, including safety, nutrition, physiology and microbiology, need to be developed and evaluated using both test animals and human test panels.

Risk assessments should involve an understanding of the mechanisms involved. We need basic information on the mechanisms of toxicity for naturally occurring substances. Inherent in this need is the requirement for basic knowledge of cell biochemical processes, but with the qualifier that mechanistic research needs to be "for cause", i.e., directed toward real, identified problems.

Relative Risks and Benefits

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III. REDUCING RISKS FROM NATURALLY OCCURRING TOXICANTS

The classes of naturally occurring toxicants considered by the workshop group included: 1) mycotoxins, 2) seafood/marine toxins, 3) plant toxins, and 4) processing-induced food toxicants.

A. Protocol for Prioritizing Naturally Occurring Toxicants

A database of natural toxicants should be developed to assemble and organize available information and identify data gaps. One of the primary uses of such a database would be to perform an analysis of known toxins in such a way as to rank-order their signficance in the diet so that priority compounds can be identified for risk reduction actions commensurate with available funds. Furthermore, once established such a database would be a significant research tool for the investigation of these compounds. Since the database concerns four core entities, i.e., dietary food components, occurrence of compounds in foods, physical attributes of compounds and the physiological activity (adverse and beneficial) of these compounds as a starting point a simple four-table structure is envisioned.

The **Compounds Table** would define the entity compounds and thus would include the compound name (cname), CA reg. Nom., molecular weight, and other physical attributes.

The **Occurrence Table** would define the instances of compounds in specific food sources and thus would contain cname, food source, genus, species, subtaxon, authority and concentration.

The **Physiological Activity Table** would define the role of a compound with respect to a specific endpoint, thus this table needs to contain at least cname, known endpoint, ED, TD, NOEL, and animal model.

The **Foods Table** needs to contain the information on food consumption patterns and thus needs to contain the dietary composition and consumption rate.

Each of these tables needs to be built individually by experts in each of these areas. While much of this information is already compiled in various databases, it is not organized appropriately for these purposes. It may well turn out that as this database is constructed, the lack of specific areas of information will become evident.

It is not predefined whether the database should be expert based (i.e., a unique value determined by a recognized expert in the field) or literature based (published values included with their citation). The former is less expensive but subject to personal bias; the latter less biased but requires a more substantial effort.

B. Research Areas for Reducing Risks

1. Prevention.

   a. Preharvest control, modulation of toxin-producing organisms, environmental factors, factors affecting toxin formation (mycotoxins, plant toxins).

   b. Identification of toxin-producing organisms (mycotoxins- fumonisins; seafood toxins- ciguatoxins, PSP, ASP).

   c. Identification of commodities susceptible to toxin contamination (mycotoxins, seafood toxins, plant toxins, processing-induced toxicants).

2. Monitoring Programs.

   a. Development of rapid, facile screening assays (mycotoxins- fumonisins, nitropropionic acid; seafood toxins - ciguatoxins, ASP, DSP, PSP: plant toxins - potato; processing-induced toxicants).

   b. Identification of bio-markers for predicting high risk harvesting/fishing areas (seafood toxins).

   c. Diversion of contaminated products to lower risk uses (mycotoxins: plant toxins).

3. Decontamination.

   a. Separation of contaminated material (mycotoxins, plant induced toxicants).

   b. Inactivation of the toxins (mycotoxins, plant-induced toxicants).

   c. Restriction of bio-availability of the toxins (mycotoxins, plant-induced toxicants).

   d. Efficacy/permanency of the process (mycotoxins).

   e. Safety evaluation of the process (mycotoxins, seafood toxins, plant toxins, processing-induced toxicants).

      1) identification of decontamination by-products;

      2) toxic/mutagenic/carcinogenic potentials of reaction products;

3) comparative biological activity;

4) bio-indicators of chronic/acute health risks.

4. Identify/Eliminate Processing-Induced Food Toxicants.

- Alternative processing.

C. Special Areas for Research

1. Reduction of harmful human health effects.

a. Induction of detoxification mechanisms.

b. Enhancement of resistance.

c. Development of antidote/antagonist/toxin removal therapy.

d. Development of diagnostic methods.

e. Induced in vivo detoxification.

2. Identification, mechanisms of action, health effects.

a. Reduction of risk due to high potency immunotoxicants in foods.

b. Reduction of risk due to neurotoxicants in foods.

c. Reduction of risk due to teratogenic toxicants in foods.

3. Cross disciplinary interagency (international) cooperative research on food toxins.

- Model of INILSEL (International Network for the Improvement of Lathyrus sativus and the Eradication of Lathyrism).

4. Natural toxicants transmitted through animal-derived foods.

5. Development of new/novel approach to study foodborne hazards/risks utilizing "food ecosystem".

6. Evaluate relative risks associated with specialty and health food items compared to traditional foods.

7. Food labeling for food safety.

8. Alternative approaches to evaluation of food safety such as effect-based in contrast to chemical-based. The targets of action would be the identification of adverse effects of foodstuffs rgardless of chemicals involved. For this effect-based approach, batteries of in vitro and in vivo bioassays for different toxic endpoints need to be developed and validated.

Reducing Risks from Naturally Occurring Toxicants

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IV. ANTITOXICANTS

A. Issues

1. Maladies - What maladies are subject to mitigation?
   What population groups should be targeted (e.g., cancer, aging, osteoporosis, atherosclerosis)?

2. Identification of mitigating agents (m.a.).

   Can we concentrate on one phase of a disease?

   Can we concentrate on certain classes or a class of chemicals?

   Must we know causes of disease in order to address identification of m.a.?

   Does general nutrition play a role in action of m.a.?

   Should folk remedies be explored as sources of potential m.a.?

   What short term tests should be used to identify m.a.?

   Should a repository be established to provide prospective m.a. to interested researchers.

3. Toxicology - How important are in depth studies of mechanism, toxic and mitigating potency and human safety of m.a.?

4. Regulatory issues - How are m.a. and natural and designed food that contain them to be regulated, or should they be regulated at all?

5. Public eduation - What are most rational, non-advocative means of educating the public on the proper role of m.a. in a healthy lifestyle?

B. Information

In contrast to the ready availability of much of the information on the cancer-causing effects of most environmental and foodborne substances, little information is readily available on m.a. for cancer or other maladies. Many studies of cancer m.a. have been completed during the last ten years and are on-going, but the results of many of these studies have yet to be published or reviewed. Information on m.a. resulting from contract work to NCI and other government agencies must be made available through the Freedom of Information Act. It is imperative that this body of work be made generally available to the scientific community.

Extensive data are available on the phytochemical contents of certain food products. Much more data are required on levels of potential m.a. in food produced, grown and

processed under various conditions. An extensive database is being developed on phytochemicals by the European Community and this base should be made international in scope.

Data on the most frequently consumed foods in the U.S. are available through the Nutrition Labeling and Education Act (N.L.E.A.).

C. Research Objectives

There is a high priority need to understand the potential of food antitoxicants to ameliorate diseases in addition to cancer. These include immune dysfunction, neurological dysfunction, inflammatory diseases, and cardiovascular diseases. Initial emphasis should be placed on human epidemology or experimental animal proof-of-concept data that indicate a probable role for antitoxicants in reducing incidence or severity of these diseases. "Molecular epidemiology" approaches evaluating effects on intermediary biomarkers may be useful as early endpoint indicators of efficacy.

For cancer, there is a continuing need for identification of new food-borne m.a.. The effects of candidate inhibitors should be examined in a variety of chemical and viral carcinogenesis protocols, using a variety of vertebrate animal models, target organs, and tumor types. The potential of m.a. individually or in combination, to mitigate the stress diet (high fat, low fiber, low D; low Ca++, high phosphate) carcinogenesis models should be explored. Increased attention should be given to the discovery of factors that can suppress the post-initiation phases of tumor promotion, progression, and metastasis. Such agents may be expected to be effective and less dependent on the factors responsible for intiating human cancer, which at present are largely unknown. The influence of food processing/preparation on these factors should be investigated. It should be recognized that NCI has a major effort in identifying new anticancer agents, and there may be little need or support for separate efforts in this field of research. However, there is a recognized need for new research, in assessing efficiency of mixtures, including those that reflect m.a. ratios in natural foods. The results of ongoing NCI research using mixtures should also be made available through N.A.S.

Research to define mechanisms of action of candidate m.a. should receive high priority. Several issues should be incorporated into experimental programs:

- Preclinical trials with healthy subjects (human or animal) should be conducted to establish m.a. chronic pharmacokinetics (uptake, distribution, and metabolism). Parameters that assess inhibitor influences on metabolic and physiologic state should be determined, including status of important drug receptors, prostaglandin synthesis pathways, phase I and phase II enzyme activities. The dose-response influence of candidate factors on overall health status should be assessed.

- Tumor studies should establish whether factors modulate initiation processes, post-initiation processes, or both. The influence of dietary intervention on pre-existing tumors, or highly metastatic tumor models should receive attention.

The dose-response efficacy for cancer inhibitors, as well as potentially harmful effects of cancer enhancement, should be established for promising individual agents. The existence of thresholds for protection should be established. Tumor protocols should determine if the protective agent can also exhibit protocol-dependent enhancement (co-carcinogenesis, promotion). If enhancing effects occur, the mechanisms and dose-response potency for these effects should be evaluated, so that benefits of protection can be compared to potential risk of enhancement. There is a need to design combined chemopreventative protocols for evaluating mixtures of agents, including mixtures that reflect the ratio of agents in foods.

There is a need to make available data, and a data base, on candidate mitgating agents in specific food items.

- A systematic effort is needed to quantify the profiles of individual candidate agents in specific commodities. Although all commodity/classes are of potential interest (spices, grains, fruits, vegetables), initial attention should be given to the 20 foods highest in consumption according to the NLEA. Attention in these studies should be given to the cultivar, growing conditions, storage conditions, and analytic methods used in each study. Investigators should recognize that chemical extraction may yield chemical profiles quantitatively and qualitatively different from those bioavailable in the human or animal digestive tract, and that digestion-based models may be useful in certain studies. The effects of food processing and preparation on profiles and individual factors should be investigated.

- A computer accessible data base, perhaps maintained by NAS, FDA, or USDA, should be constructed for food-related factors having known or potential inhibitory effects. The data base could include conventional foods, both fresh and processed, and traditional herbal remedies. Important information would include plant species, cultivar, growing and storage conditions, reference to extraction and analytical methods used, names, structures and quantity (plant concentration) of each candidate chemical identified. The data base should include references to peer-reviewed studies on the inhibitory efficacy in in vitro screening, whole animal, or human studies for each compound in the data base. The data base could be maintained and updated as contributors issue manuscripts approved for publication. Related data bases that could be incorporated already exist, or are in preparation (e.g., Roger Fenwick is working through the European Economic Community to create an analytic data base).

D. Research Priorities

A broad-based study should be conducted to test the role of dietary antioxidants and other tumor-suppressing agents as cancer m.a. These studies should include analyses of mechanism, safety, dose response, and quantities of m.a. in foods as consumed.

This research will require the combined efforts of toxicologists, chemists, food scientists, nutritionists, and extension specialists.

Lower priority should be given to analytical and database studies.

E. Cooperators

The food industry along with government agencies (NIH, USDA) should be interested in supporting the proposed broad based studies.

F. Funding

Various agencies of government interested in public health and industries working with food can be sources of funding.

G. Alternative Approaches

Work should be done as much as possible based on investigator initiated projects and less emphasis should be placed on contractual work.

Antitoxicants

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V. ANALYTICAL CONSIDERATIONS FOR NATURALLY OCCURRING TOXICANTS AND ANTITOXICANTS

The workshop group believed that chemical constituents of food can be either beneficial or detrimental and that analytical techniques should be able to quantitate all components. Analyses of the naturally occurring toxic or antitoxic constituents of foods must be an important part of any interdisciplinary evaluation of food safety.

A. Issues

Three major issues were identified by the working group:

1. The changes occurring in a food because of genetic alterations through traditional breeding or biotechnology means must be chemically identified and quantitated. The chemical changes brought about by the processes of manufacturing and preparing foods must also be identified.

2. The concentrations of known toxicant and antitoxicant components of currently available foods must be determined to establish the benchmarks to be used to document changes in genetically altered, manufactured, or processed foods.

3. Established and genetically altered foods must be compared and chemically characterized, "fingerprinted," for compounds with a molecular weight of 5000 or below. Those compounds showing large changes must be chemically identified to evaluate potential detrimental or beneficial effects.

B. State-of-the-Art in Analytical Chemistry

1. The participants felt that the state-of-the-art methodology for identification and structural identification is good. However, appropriate methods are not always used in food analysis.

2. Current analytical technology is very good but specific methods for many toxicants and antitoxicants must be developed or improved for use in the assay of foods. There are relatively few validated methods for many of the relevant compounds and great emphasis must be placed on appropriate validation of analytical methods. The newer immunochemical techniques such as ELISA and immunoaffinity chromatography should be adapted for use in food safety studies. Analytical chemists should be encouraged to work closely with their colleagues in developing immunochemical methods.

3. Methods for "fingerprinting" compounds below 5000 molecular weight are weak and need significant improvement. New methods that separate and quantitate compounds by molecular weight and solubility need to be developed.

C. Research Objectives

The workshop group members identified two research objectives:

1. To improve or develop validated analytical methods for the determination of the toxic and antitoxic constituents of foods.

2. To develop and improve the techniques for "fingerprinting" the components of food.

D. Recommendations

The workshop group believed that analytical chemistry and structural elucidations are difficult and expensive. Many experts are needed to plan, implement and accomplish the analytical needs of food safety. The infrastructure for this work currently does not exist. Therefore, CSRS and the FNB should develop and initiate a national program to provide coordination and leadership in developing the analytical chemistry infrastructure related to the determination of the toxic and antitoxic chemicals in foods. Funding should be provided by the USDA, NIH and other appropriate federal agencies. Research on the toxic and antitoxic chemicals should be funded under the USDA National Research Initiative program in food safety. CSRS should request assistance from appropriate professional organizations, industries, government agencies, and universities in identifying research scientists. Once identified, research groups could be formed to address specific issues. A national interregional project would probably be most appropriate.

E. Other Issues

Other issues that should be addressed include professional training in food safety; the establishment of a national database on chemical constituents of foods; publication of relevant facts in the popular press as well as in the scientific press; and, above all, education of the public in the real risks which must be addressed in food safety issues.

Analytical Considerations for Naturally Occurring
Toxicants and Antitoxicants

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CONCLUSIONS

New technologies and global markets will expand the nature of foods available to U.S. consumers. It is imperative that the scientific and regulatory communities ensure that information is available that will assure that these foods portend neither real nor perceived threats to health. Though natural toxicants do not engender fear in the public the way pesticides do, research in this area and on the potential benefits of natural antitoxicants may have a much greater impact on health and disease prevention.

The workshop participants concluded that the topic of naturally occurring toxicants and antitoxicants in foods warrants a national research effort and national coordination. There is a need for a coordinated database of these compounds. We need to better understand the effects on human health of long term, low level exposure to these compounds. Better means of detecting and reducing exposure to toxicants need to be addressed. We need to better understand the mechanisms that cause some compounds to act as toxicants or antitoxicants under different circumstances. Though the mechanisms in place are believed to be adequate to assure safety of biotechnology-derived foods, genetic modification may be used to select food crops with low levels of toxicants yet also contain natural compounds that may have disease- prevention or therapeutic effects. We need to find ways to estimate the effects, risks and benefits of these compounds in the complex matrix of foods. There is a high priority need to understand the potential of antitoxicants to ameliorate diseases other than cancer.

Targeted and multifaceted funding should be made available to undertake a coordinated multidisciplinary and interdisciplinary research effort involving agricultural production scientists, food and nutrition scientists, and public health scientists. This research effort should be coordinated through a broad-based advisory body of government, university and private sector scientists and policy makers. International linkages should be sought. Such an effort will contribute to the public's confidence in the food supply and enhance our understanding of the way in which food affects health.

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NATURALLY OCCURRING SUBSTANCES IN TRADITIONAL AND BIOTECHNOLOGY-DERIVED FOODS: THEIR POTENTIAL TOXIC AND ANTITOXIC EFFECTS

MARCH 9-11, 1992

NATIONAL ACADEMY OF SCIENCES
INSTITUTE OF MEDICINE, FOOD AND NUTRITION BOARD

ARNOLD AND MABEL BECKMAN CENTER AUDITORIUM
IRVINE, CA

SYMPOSIUM PROGRAM

MONDAY, MARCH 9, 1992

Dietary Risks of Naturally Occurring Toxicants

Morning Session: Purpose and Overview of Dietary Risks

Moderator: Joseph Rodricks, Environ Corporation

8:30 Introduction and Purpose of Symposium
...Catherine E. Woteki, Food and Nutrition Board

8:45 Dietary Factors: Their Significance in the Etiology of Diseases
...Paul LaChance, Rutgers University

9:15 Overview of Toxicant Risks: Their Occurrence and Dietary Levels
...Michael Pariza, University of Wisconsin

9:45 Overview of Mycotoxin Risks
...Dennis P.H. Hsieh, University of California, Davis

10:15 Break

10:30 Carcinogenic Toxicants in Foods: Their Relation to Other Food-Borne Risks
...Robert Scheuplein, Food and Drug Administration

11:00 Heterocyclic Amine Mutagens and Carcinogens in Foods
...Jim Felton, Lawrence Livermore Laboratory

11:30 The Effects of Estrogens and Other Developmental Toxicants in Foods
...John McLaughlin, National Institute of Environmental Health Sciences

12:00 Lunch

Early Afternoon Session: Naturally Occurring Toxicants in Foods

Moderator: John Kinsella, University of California, Davis

1:00 Balancing Toxicant Risks and Antitoxicant Benefits in Foods
...Bruce Ames, University of California, Berkeley

1:30 Acute and Chronic Effects of Food-Borne Neurotoxicants
...Peter Spencer, Oregon State Health Sciences University

2:00 The Dietary Impact of Phytates and Other Antinutrients
...Barbara Schneeman, University of California, Davis

2:30 The Effects of Food Processing on Toxicant Risks
...Takayuki Shibamoto, University of California, Davis

3:00 Break

Late Afternoon Session: Relevant Benefits of Antitoxicants in Foods

Moderator: Richard Hall

3:15 Antimutagenic and Anticarcinogenic Agents in Foods
...George Bailey, Oregon State University

3:45 Cholesterol Biosynthesis Inhibitors in Foods
...Judy Marlett, University of Wisconsin

4:15 The Antiallergic Effects of Plant Flavonoids
...Elliott Middleton, SUNY, Buffalo

4:45 Food Phytochemicals and Their Potential Anticarcinogenic Activity
...Herbert Pierson, Food Phytochemical Research Institute

5:15 When Does a Natural Component of Food Become a Hazard?
...Sanford Miller, University of Texas, San Antonio

5:45 Reception

6:30 Dinner

continued

TUESDAY, MARCH 10, 1992

Biotechnology: Relevant Risks for New Foods Under Development

Morning Session: Biotechnology: New Food Products Under Development

Moderator: Ralph Hardy, Boyce Thompson Institute, Cornell University

9:00 The Potential for Toxicants in Transgenic Plants
...Ralph Hardy, Boyce Thompson Institute, Cornell University

9:30 The Potential for Toxicants in Transgenic Animals
...Floyd Byers, Texas A & M University

10:00 Adjusting Risks to Toxicants and Antitoxicants by Genetic Manipulation
...Peter Day, Cook College, Rutgers University

10:30 Break

11:00 Biotechnology-Derived Food Ingredients
...Susan Harlander, University of Minnesota

11:30 Chemical and Biochemical Assays for Natural Substances
...Kent Stewart, Virginia Polytechnical Institute

12:00 Toxicants and Antitoxicants: Peering Ahead Toward the Future
...Richard Hall

12:30 Lunch

WORKSHOP PROGRAM

2:00 Introduction: Background, Purpose, Scope, Structure, Procedures
...Frank Flora, CSRS/USDA

2:30 Group Discussion on Workshop Purpose, Scope, Structure, Procedures

3:00 Breakout Groups Led by Group Discussion Leaders:

I. Known Toxicants
II. Antitoxicants
III. Impact of Genetic Engineering and Biotechnology on Naturally Occurring Toxicants
IV. Methodologies
V. Relative Risks and Benefits (Health, Economics)
VI. Reducing Risks from Naturally Occurring Toxicants

5:00 Adjourn

WEDNESDAY, MARCH 11, 1992

9:00 Reconvene Working Groups to Assess State of the Science, Identify Research Needs, and Develop Researchable Objectives

12:00 Lunch

1:30 Reports from Working Groups

3:30 Group Discussion/Action Plan Development

5:00 Summary/Conclusions

5:15 Adjourn

NATURALLY OCCURRING SUBSTANCES IN TRADITIONAL AND BIOTECHNOLOGY-DERIVED FOODS: THEIR POTENTIAL TOXIC AND ANTITOXIC EFFECTS

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SPONSORED BY

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